09/913944

PATENT COOPERATION TREATY

REC'D 27 APR 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P 405 PC00		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK00/00065	17/02/2000	17/02/1999
International Patent Classification (IPC) or national classification and IPC A61L27/00		
Applicant SURFARC APS		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 11 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/09/2000	25.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schnack, A Telephone No. +49 89 2399 8149

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/DK00/00065

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-73	as originally filed				

Claims, No.:

1-89	as received on	11/04/2001	with letter of	11/04/2001	

Drawings, sheets:

1/31-31/31	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 69.

because:

☒ the said international application, or the said claims Nos. 69 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-69

	No:	Claims	(see seperate sheet)
Inventive step (IS)	Yes:	Claims	1-69
	No:	Claims	(see seperate sheet)
Industrial applicability (IA)	Yes:	Claims	1-68, 70-89
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: Biomaterials, vol. 19, 1998, pp. 953-960
D2: Biomaterials, vol. 12, 1991, pp. 144-153
D3: Journal of Biomedical Materials Research, vol. 25, 1991, pp. 829-843
D4: Macromolecules, vol. 31, 1998, pp. 5059-5070
D5: Journal of Biomedical Materials Research, vol. 35, 1997, pp. 1-8
D6: J. Biomater. Sci. Polymer Edn., vol 7, no. 10, 1996, pp. 839-855
D7: WO 97 18 904

Section III
Non-establishment of opinion

Claim 69 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Section V
V.1. Novelty
Remarks under Article 33(2) PCT:

The present subject matter relates to a material comprising a substratum, said substratum is "contacted" by at least one macromolecule. The claim further appears to specify the degree of said contact in terms of contact angles. Thus, for a specific substrate and a specific macromolecule, the ratio R is dependent on the degree to which the substratum is saturated with the macromolecule.

It appears that the feature, which is claimed to distinguish the present subject matter from the prior art is the value of the ratio R, which is claimed to be: $0 \leq R < 0.4$. Furthermore the resulting contact angle, a, is specified to be 60-125 degrees. Applicant claims that prior art biocompatible materials all have contact angle, which are below 60

degrees. and that prior art R values in relation to non-biological materials covered with e.g. PEG would be higher than the presently specified 0.4.

The characterizing features of present claim 70 does not necessarily lead to a material as claimed in present claims 1-55. The characterizing features of present claim 70 are not novel in view of the prior art, since "providing a substratum having a second advancing contact angle and contacting said substratum with a composition comprising a plurality of macromolecules" is clearly not novel, (see all documents cited in the search report). Thus, the subject matter according to present claim 70 lacks novelty.

However, with respect to the documents cited in the search report, the following observations are made:

D1 discloses PEG immobilized silicon surfaces. On page 956, first col., second paragraph, contact angles are disclosed. The contact angle for unmodified silicon was less than 10 degrees and the contact angles for PEG modified silicon surfaces were in the range 15-20 degrees. This means that PEG modification of the surface imposes a higher value of contact angle as compared to unmodified silicon. However, the resulting contact angles are far below 60 degrees as specified in present claim 1. Calculating the present R-value, it appears that this would also fall not fall within the scope of present claim 1:

a = e.g. 15 degrees
b_0 = 10 degrees
b_{sat} = not mentioned, but must be assumed to be in more than 20 degrees, e.g. 30 degrees

Thus, e.g. $R= (10-15)/(10-20) = 0.5$ or
$R = (10-15)/(10-30) = 0.25$

Thus, it appears that the subject matter according to present claim 1 is novel in view of D1.

D2 does not appear to disclose materials falling within the scope of present claim 1, since it appears that the materials according to D2 are modified to an extend, which fall

outside the scope of present claim 1, i.e. the contact angles are modified so much that it appears that the surfaces are almost saturated with the macromolecule. This is however, not explicitly stated in D2, since the value b_{sat} does not appear to be disclosed in D2, (see D2, page 146-147, **Contact angles**). The same observations appear to apply for D3 and D5.

D4 describes results of studies, where varying amounts of PEO has been grafted onto silicone surfaces. D4 does not appear to disclose any contact angle measurements. However, samples comprising different grafting densities of the PEO on the substrate are disclosed, (see D4, the abstract). Thus, in the absence of contact angle measurements, it appears that novelty must also be acknowledged in view of D4.

D6 states that incomplete coverage of some samples of PEO grafted silicone membranes has led to a relative high contact angle, (see D6, page 846-847 *Contact angle measurement*). However, no explicit disclosure of contact angles of modified surfaces higher between 60 and 125 degrees appears to be presented in D6 and it furthermore that high contact angles are said to be less preferable. Thus, novelty appears to be acknowledgeable in view of D6.

D7 discloses materials having a monolayer of PEO molecules. No contact angle measurements appears to be disclosed and applicant claims that the materials according to D7 would not to fall within the scope of present claim 1, because the resulting contact angle would be less than 60 degrees.

The other references cited in the search report also relate to hydrophobic substrates, which have been modified in order to render the surface more hydrophilic so as to increase the biocompatibility. However, in view of the presently used parameters, (contact angles), it appears to be impossible to determine whether the subject matter according to these references anticipates the present subject matter. Applicant has however, in his letter of reply argued that none of these references disclose biocompatible materials having contact angles of less than 60 degrees.

V.2. Inventive step

Remarks under Article 33(3) PCT:

The present subject matter appears to reside in the allegation that contacting a substrate with a macromolecule to an extend, which results in contact angles of 60-125 degrees and which changes the contact angle of the surface up to 40% of the possible change, (saturation), is directly linked to an advantageous effect with regard to biocompatibility. Since it appears that prior art materials of the present type all have contact angles, which are below 60 degrees, it appears that an inventive step can be acknowledged, since no prior art reference appears to suggest the present advantageous properties of the present materials having a contact angle of 60-125 degrees, (cf. present page 65, lines 20-32, page 68, lines 7-9 and figure 11). However, it appears that further elucidation of the link between resulting contact angle, a, and biocompatibility, must be provided the subsequent national/regional phase.

V.3. Industrial applicability

Remarks under Article 33(4) PCT:

For the assessment of the present claim 69 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Section VIII

Remarks under Article 5 and 6 PCT:

Further elucidation of the alleged link between contact angles and contact angle changes and solution to the technical problem of protein denaturation, appears to be necessary, since these features are the only features, which characterize the present invention.

Under this, it does not appear to have been sufficiently demonstrated that all thinkable substrates, which have been modified with any thinkable macromolecule to an extend

as presently claimed, would solve the technical problem. Only one specific method of modification, (photo-grafting), with one specific macromolecule, (PEG), has presently been used, (and no unambiguous and direct link between the presently claimed change in contact angle, (up to 40%) compared to the unmodified substratum and solution to the technical problem appears to have been demonstrated.

The present subject matter appears furthermore not to be sufficiently disclosed for the skilled man throughout the whole scope of the claims, because the skilled man would not know how to reach the claimed contact angle a, for other substrates and for other macromolecules than the ones presently exemplified.

Patent claims

1. Biocompatible material comprising a substratum contacted by at least one macromolecule,

   said material having a first advancing contact angle a in the range of from 60 to 125 degrees,

   said substratum having a second advancing contact angle b_0 when not contacted by a macromolecule, and another second advancing contact angle b_{sat}, when said substratum is saturated by said macromolecules,

   wherein said advancing contact angles are measured using water and air saturated by water vapour,

   wherein b_{sat} essentially does not change when the substratum is contacted by further macromolecules by means of a chemical bond,

   wherein the relation between said advancing contact angles is as defined by the ratio R,

$$R = (b_0 - a) / (b_0 - b_{sat})$$

   and wherein the numerical value of R is in the interval from and including 0 to less than 0.4.

2. Material according to claim 1, wherein said substratum comprises a hydrophobic polymer.

3. Material according to claim 2, wherein said substratum has an advancing contact angle of more than 90 degrees.

4. Material according to any of claims 1 to 3, wherein said macromolecule comprises an amphiphilic polymer.

5. Material according to claim 1, wherein the substratum is further contacted by a plurality of soluble substances capable of forming a self-assembled monolayer comprising at least one macromolecule.

6. Material according to claim 5, wherein said soluble substances are n-alkane chains preferably containing from 8 to 24 carbons.

7. Material according to any of claims 1 to 6, wherein said substratum is pretreated or modified, preferably by contacting the substratum with a charged group or a hydrophilic compound.

8. Material according to claim 1, wherein said first advancing contact angle is in the range of from 70 degrees to 120 degrees.

9. Material according to claim 8, wherein said first advancing contact angle is in the range of from 75 degrees to 110 degrees.

10. Material according to claim 8, wherein said first advancing contact angle is in the range of from 80 degrees to 100 degrees.

11. Material according to any of claims 1 to 4, wherein said ratio is in the range of from 0 to less than 0.30.

12. Material according to claim 11, wherein said ratio is in the range of from 0 to less than 0.20.

13. Material according to claim 11, wherein said ratio is in the range of from 0 to less than 0.10.

14. Material according to claim 11, wherein said ratio is in the range of from 0 to less than 0.05.

15. Material according to any of claims 1 to 4, wherein the first advancing contact angle a is substantially identical to the advancing contact angle b_D.

16. Material according to any of the preceding claims, wherein said material, when contacted by a first determinant comprising a compound selected from the group consisting of a polypeptide, or part thereof, a nucleic acid moiety, a carbohydrate moiety, and a lipid moiety, including any combination thereof, is capable of maintaining said compound in a biologically active form.

17. Material according to claim 16 wherein said compound is a polypeptide or part thereof.

18. Material according to claim 16 or 17 further comprising said first determinant comprising said compound, wherein said first determinant is maintained in a biologically active form when contacted by said substratum and/or said macromolecule.

19. Material according to claim 18 wherein said biologically active form is essentially a biologically active conformation.

20. Material according to any of claims 15 to 19 wherein said biologically active form or conformation is maintained and/or improved and/or stabilized by means of the cooperativity of said substratum and said macromolecule.

21. Material according to claim 15 to 19 wherein said biologically active form or confirmation is maintained and/or improved and/or stabilized when contacted by said substratum and said macromolecule.

22. Material according to any of the preceding claims, wherein the weight increase per area unit arising from the part of the macromolecule essentially consisting of PEG or poly(ethylene oxide) (PEO) is less than 2.0×10^{-22} grams (g) per square nanometer (nm^2).

23. Material according to claim 22, wherein said difference is less than 0.3×10^{-22} grams (g) per square nanometer (nm^2).

24. Material according to any of claims 1 to 23, wherein said substratum is at least substantially flexible.

25. Material according to claim 24, wherein said substratum is a film.

26. Material according to any of claims 1 to 23, wherein said substratum is essentially rigid or at least substantially non-flexible.

27. Material according to claim 26, wherein said substratum comprises a crystalline structure capable of supporting a self-assembled monolayer such as gold, silicon oxide, and similar crystalline structures and/or structures that are smooth on a nanometer scale.

28. Material according to any of the preceding claims, wherein said macromolecule has a MW of more than 400 Da.

29. Material according to claim 28, wherein said macromolecule has a MW of more than 5.000 Da.

30. Material according to claim 28, wherein said macromolecule has a MW of more than 10.000 Da.

31. Material according to any of the preceding claims, wherein said macromolecule is a conjugate comprising a head group, a guiding group, a linker group, a polymer chain or a main body, and a functional end group.

32. Material according to claim 31, wherein said head group is capable of adsorbing onto the substratum.

33. Material according to claim 32, wherein said head group is capable of forming an ionic bond.

34. Material according to claim 32, wherein said head group is capable of forming a self-assembled monolayer.

35. Material according to claim 32, wherein said head group is capable of forming a chemical bond.

36. Material according to claim 32, wherein said head group is entangled into or with the substratum.

37. Material according to claim 31, wherein said guiding group is a bifunctional group comprising an aliphatic, linear or weakly branched group.

38. Material according to claim 31, wherein said linker group is capable of being enzymatically or chemically hydrolyzed.

39. Material according to claim 31, wherein said linker group is essentially stable against cleavage under practical circumstances.

40. Material according to claim 31, wherein said polymer chain or main body is preferably hydrophilic, uncoiling in an aqueous environment and exhibiting an excluded volume.

41. Material according to claim 31, wherein said functional end group is capable of linking permanently or reversibly other biological or synthetic molecules or materials.

42. Material according to any of claims 16 to 21, wherein said biologically active compound is selected from the group consisting of membrane associated and/or extracellular matrix polypeptides natively produced by a microbial cell, a plant cell or a mammalian cell.

43. Material according to claim 42 wherein said biologically active compound is selected from the group consisting of a polypeptide, an antibody, a polyclonal antibody, a monoclonal antibody, an immunogenic determinant, an antigenic determinant, a receptor, a receptor binding protein, an interleukine, a cytokine, a cellular differentiation factor, a cellular growth factor, and an antagonist to a receptor.

44. Material according to claim 42, wherein said biologically active compound is a synthetic polypeptide, or part thereof, capable of contacting said substratum and/or said macromolecule.

45. Material according to claim 42, wherein said biologically active compound is a synthetic polypeptide, or part thereof, capable of contacting said substratum and said macromolecule.

46. Material according to claim 42, wherein said biologically active compound is an adhesion polypeptide, preferably fibronectin or vitronectin.

47. Material according to any of claims 42, wherein said biologically active compound results in an improved contact between said material and a biological entity, such as a biological cell or a virus, or part thereof, including a polypeptide, or a part thereof, a nucleic acid moiety, a carbohydrate moiety, and a lipid moiety, including any combination thereof.

48. Material according to any of the preceding claims, said material further comprising a second determinant.

49. Material according to claim 48, wherein said second determinant comprises a biological entity, such as a biological cell or a virus, or part thereof, including a polypeptide, or a part thereof, a nucleic acid moiety, a carbohydrate moiety, and a lipid moiety, including any combination thereof.

50. Material according to claim 49, wherein said biological entity is selected from the group consisting of a polypeptide, an antibody, a polyclonal antibody, a monoclonal antibody, an immunogenic determinant, an antigenic determinant, a receptor, a receptor binding protein, an interleukine, a cytokine, a differentiation factor, a growth factor, and an antagonist to the receptor.

51. Material according to claim 49, wherein said biological cell, or part thereof, is selected from the group consisting of a mammalian cell, including a human cell and an animal cell, a plant cell, a microbial cell, including a eukaryotic microbial

cell, including a yeast and a fungus, and a prokaryotic microbial cell including a bacteria.

52. Material according to claim 51 wherein said biological cell is a mammalian cell.

53. Material according to any of the preceding claims, wherein said substratum is porous and preferably a membrane.

54. Material according to claim 53, wherein the flux of water through said material is substantially unchanged as compared to the flux of water through said porous substratum.

55. Material according to any of claims 1 to 52, wherein said substratum is non-porous and/or substantially non-penetrable to water.

56. Material according to any of the preceding claims for use in a method of controlling cellular growth and/or cellular proliferation and/or cellular differentiation ex vivo.

57. Material according to any of the preceding claims for use in a method of separating and/or isolating biological material ex vivo.

58. Material according to any of claims 1 to 55 for use in a diagnostic method carried out on the human or animal body.

59. Material according to any of claims 1 to 55 for use in a method of therapy carried out on the human or animal body.

60. Material according to any of claims 1 to 55 for use in a method of surgery carried out on the human or animal body.

61. Material according to any of claims 1 to 55 for use as a carrier for in vivo delivery of a medicament to a human or animal body in need of said medicament.

62. Pharmaceutical composition comprising the material according to any of claims 1 to 55 and a pharmaceutically active ingredient and optionally a pharmaceutically active carrier.

63. Use of the material according to any of claims 1 to 55 or the pharmaceutical composition according to claim 62 in a method of controlling cellular growth and/or cellular proliferation and/or cellular differentiation ex vivo.

64. Use of the material according to any of claims 1 to 55 or the pharmaceutical composition according to claim 62 in a method of separating and/or isolating biological material ex vivo.

65. Use of the material according to any of claims 1 to 55 or the pharmaceutical composition according to claim 62 in a method of producing a biohybrid organ ex vivo.

66. Method of controlling cellular growth and/or cellular proliferation and/or cellular differentiation ex vivo, said method comprising the steps of contacting a cell with the material according to any of claims 1 to 55, or the pharmaceutical composition according to claim 62, and incubating said cell and said material under conditions allowing said cell to grow and/or proliferate and/or differentiate.

67. Method of separating and/or isolating biological material ex vivo, said method comprising the steps of contacting said biological material to be separated and/or isolated with the material according to any of claims 1 to 55, or the pharmaceutical composition according to claim 62, and incubating said biological material and said material under conditions that allow separation and/or isolation.

68. Method of producing a biohybrid organ ex vivo, said method comprising the steps of contacting biohybrid organ cells with the material according to any of claims 1 to 55, or the pharmaceutical composition according to claim 62, and incubating said biohybrid organ cells under conditions allowing the production of said biohybrid organ.

69. Method of in vivo delivery of a medicament to a human or animal body in need of said medicament, said method comprising the steps of contacting said body with the pharmaceutical composition according to claim 62 and incubating said body contacted by said pharmaceutical composition under conditions allowing delivery of said medicament.

70. Method for producing the material according to any of claims 1 to 55, said method comprising the steps of i) providing a substratum having a second advancing contact angle, and ii) contacting said substratum with a composition comprising a plurality of macromolecules.

71. Method according to claim 70, wherein said substratum comprises a hydrophobic polymer.

72. Method according to claim 70, wherein said substratum is pretreated prior to being contacted by said macromolecule.

73. Method according to claim 70, wherein said pretreatment is effective in increasing the wettability of said substratum.

74. Method according to claim 70, wherein said macromolecule comprises a hydrophilic polymer.

75. Method according to claim 70, wherein said macromolecule comprises a latently reactive polymer.

76. Method according to claim 70, wherein macromolecule has a MW of more than 400 Da.

77. Method according to claim 70, wherein said macromolecule comprises a conjugate comprising a cross likable head group, a linker group, a polymer chain, and a functional end group.

78. Method according to claim 77, wherein said cross linkable head group is a photo-reactive aryl azide head group.

79. Method according to claim 77, wherein said macromolecule further comprises a modifying agent.

80. Method according to claim 79 wherein said modifying agent is capable of contacting said substratum and forming a self assembled monolayer.

81. Method according to any of claims 70 to 80 for producing the material according to any of claims 1 to 55, said method comprising the further step of contacting said material with a first determinant comprising a biologically active compound.

82. Method according to claim 81, wherein said biologically active compound is selected from the group consisting of a polypeptide, an antibody, a polyclonal antibody, a monoclonal antibody, an immunogenic determinant, an antigenic determinant, a receptor, a receptor binding protein, an interleukine, a cytokine, a cellular differentiation factor, a cellular growth factor, and an antagonist to a receptor.

83. Method according to claim 81, wherein said biologically active compound is a membrane associated and/or extracellular matrix polypeptide natively produced by a microbial cell, a plant cell or a mammalian cell.

84. Method according to any of claims 81 to 83 for producing the material according to any of claims 1 to 55, said method comprising the further step of contacting said material with a second determinant comprising a biological entity.

85. Method according to claim 84, wherein said biological entity comprises a cell or a virus, or a part thereof.

86. Method according to claim 85, wherein said cell, or part thereof, is selected from the group consisting of a mammalian cell, including a human cell and an animal cell, a plant cell, a microbial cell, including a eukaryotic microbial cell, including a yeast and a fungus, and a prokaryotic microbial cell including a bacteria.

87. Method according to claim 85, wherein said virus, or part thereof, is selected from a mammalian virus, including a human virus and an animal virus, a plant virus, a microbial virus, including a eukaryotic microbial virus, including a yeast virus and a fungal virus, and a prokaryotic microbial virus including a bacteriophage.

88. Method according to claim 84, wherein said biological entity comprises a polypeptide, or a part thereof, a nucleic acid moiety, a carbohydrate moiety, and a lipid moiety, including any combination thereof.

89. Method according to claim 84, wherein said biological entity is selected from the group consisting of a polypeptide, an antibody, a polyclonal antibody, a monoclonal antibody, an immunogenic determinant, an antigenic determinant, a receptor, a receptor binding protein, an interleukine, a cytokine, a differentiation factor, a growth factor, and an antagonist to the receptor.